Retinoic Acid and Affective Disorders: The Evidence for an Association

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ABSTRACT

Objective: Isotretinoin (13-*cis*-retinoic acid), approved by the US Food and Drug Administration for the treatment of acne, carries a black box warning related to the risk of depression, suicide, and psychosis. Retinoic acid, the active form of vitamin A, regulates gene expression in the brain, and isotretinoin is its 13-*cis* isomer. Retinoids represent a group of compounds derived from vitamin A that perform a large variety of functions in many systems, in particular the central nervous system, and abnormal retinoid levels can have neurologic effects. Although infrequent, proper recognition and treatment of psychiatric side effects in acne patients is critical given the risk of death and disability. This article reviews the evidence for isotretinoin's relationships with depression and suicidality.

Data Sources: The PsycINFO, MEDLINE, and PubMed searchable database indexes were searched for articles published in the English language from 1960 to June 2010 using the key words *isotretinoin*, *retinoids*, *retinoic acid*, *depression*, *depressive disorders*, and *vitamin A*. Evidence examined includes (1) case reports; (2) temporal association between onset of depression and exposure to the drug; (3) challenge-rechallenge cases; (4) class effect (other compounds in the same class, like vitamin A, having similar neuropsychiatric effects); (5) dose response; and (6) biologically plausible mechanisms.

Study Selection: All articles in the literature related to isotretinoin, depression, and suicide were reviewed, as well as articles related to class effect, dose response, and biologic plausibility.

Data Extraction: Information from individual articles in the literature was extracted, including number of episodes of depression, suicidality, suicide, psychosis, violence and aggression, past psychiatric history, time of onset in relation to isotretinoin usage, medication dosage, duration of treatment, and dechallenge and challenge history.

Results: The literature reviewed is consistent with associations of isotretinoin administration with depression and with suicide in a subgroup of vulnerable individuals.

Conclusions: The relationship between isotretinoin and depression may have implications for a greater understanding of the neurobiology of affective disorders.

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Isotretinoin (13-*cis*-retinoic acid) is a medication for the treatment of acne that has been associated with psychiatric side effects, including depression, suicide, aggression, and psychosis. Isotretinoin is a retinoid that occurs naturally in the body; retinoids are a group of molecules derived from vitamin A that are essential in regulating the function of multiple organ systems in the embryonic and adult mammal.[1] The majority of these functions are performed by the vitamin A metabolite all-*trans* retinoic acid, which binds to retinoid receptors to control gene transcription.[2] Retinoic acid has a number of functions, which include regulation of brain development in utero; thus, administration of retinoids (including isotretinoin) during pregnancy is associated with neurologic side effects.[3–5]

Isotretinoin works for the treatment of acne in part by inhibiting sebaceous gland function, as well as decreasing keratinization, and suppressing the inflammatory response. The US Food and Drug Administration (FDA) has approved this drug for the treatment of cystic and nodular acne that is not responsive to other forms of treatment.[6–8] Isotretinoin is the same molecule as the transcriptionally active form of retinoic acid, all-*trans* retinoic acid, but is altered subtly in shape (ie, is an isomer) by having one of its double bonds, at the 13th carbon, in *cis* conformation. Isotretinoin is an endogenous isomer of retinoic acid and can be present at similar concentrations in the plasma as all-*trans* retinoic acid.[9] It is the all-*trans* isomer of retinoic acid that has a high affinity for the retinoic acid receptor to regulate transcription, and the bioactivity of isotretinoin is most likely achieved via isomerization in tissue to all-*trans* retinoic acid.[10,11] Although this implies the activity of isotretinoin is less than that of the all-*trans* isomer, isotretinoin is more resistant to catabolism and has an elimination half-life of 20 hours, in contrast to only 0.9 hours for all-*trans* retinoic acid, and the peak plasma concentrations for isotretinoin are reached 2–4 hours after oral dosage.[12] The side effect profile of isotretinoin led it originally to be approved for only severe nodular or cystic acne; however, dermatologists in the United States have frequently prescribed it for less severe acne.[8] For instance, in 1999, of patients treated with isotretinoin only about 8% suffered severe acne, while the majority had mild to moderate acne.[8]

Recently, there has been increased attention to the potential psychiatric side effects of isotretinoin.[13–26] This interest is related to the increase in warnings since its first introduction, including the application of a black box warning for suicide, depression, aggression, and psychosis as well as the institution of the iPLEDGE program, a required registry of manufacturers, pharmacists, patients, and doctors established by the FDA in 2005.[27]

In this article, we discuss the evidence for an association between isotretinoin and depression. The neurobiology of retinoids as they relate to affective disorders, which is the basis for the biologic plausibility component of assessing the effects of isotretinoin on depression, was extensively discussed in our earlier review.[28] The focus of the current article is the clinical literature supporting associations of isotretinoin with suicide and with depression; however, we also review new biologic research performed since the time of that review as well as studies in humans on the effect of isotretinoin

on metabolic pathways associated with depression as well as effects of isotretinoin on the human central nervous system.

DATA SOURCES AND STUDY SELECTION

The PsycINFO, MEDLINE, and PubMed searchable database indexes were searched for articles published in the English language from 1960 to June 2010 using the key words *isotretinoin*, *retinoids*, *retinoic acid*, *depression*, *depressive disorders*, and *vitamin A*. Evidence examined includes (1) case reports; (2) temporal association between onset of depression and exposure to the drug; (3) challenge-rechallenge cases; (4) class effect (other compounds in the same class, like vitamin A, having similar neuropsychiatric effects); (5) dose response; and (6) biologically plausible mechanisms. All articles in the literature related to isotretinoin, depression, and suicide were reviewed, as well as articles related to class effect, dose response, and biologic plausibility.

Information from individual articles in the literature was extracted, including number of episodes of depression, suicidality, suicide, psychosis, violence and aggression, past psychiatric history, time of onset in relation to isotretinoin usage, medication dosage, duration of treatment, and dechallenge and challenge history.

RESULTS

Neuropsychiatric Effects of Vitamin A

Referring to the spectrum of retinoids used in the pharmacologic treatment of dermatologic disorders, Silverman et al,[29] in their 1987 article entitled "Hypervitaminosis A Syndrome: A Paradigm of Retinoid Side Effects," stated that,

> although each new retinoid is developed with the aim of maximizing specific therapeutic effects and minimizing toxicity, the fact remains that the major side effects of retinoid treatment are those of hypervitaminosis A syndrome. There appear to be no "new" side effects or toxicities encountered during the clinical use of first-, second-, or third-generation retinoids that cannot be found in the hypervitaminosis A literature.[29(p1027)]

Hypervitaminosis A was described as being "most commonly" associated with symptoms of lethargy, depression, cyclothymia, insomnia and hypersomnolence, skin changes, hair loss, headache, bone and joint pain, and liver enlargement.[29] It was also noted that it could cause irritability and frank psychosis. The authors noted that mental symptoms could be subtle and not attributed by the patients to hypervitaminosis A, and, therefore, clinicians should specifically ask about them. Other retinoids have also been associated with depression (in one case with a positive rechallenge)[30] as well as with suicidality,[31] providing evidence for a "class effect," or common occurrence of side effects, with the retinoids.

A number of cases have been reported in the literature of mental symptoms associated with vitamin A toxicity, including irritability, depression, lethargy, mood lability, and psychosis.[32–40] These symptoms resolve with discontinuation of vitamin A.[37,39,41–43] For instance, Restak[41] reported a case of vitamin A toxicity associated with the development of aggression, personality changes, and depression, which resolved with discontinuation. McCance-Katz and Price[44] reported a case of chronic vitamin A intoxication that was associated with a 1-year history of depressed mood, poor concentration, tearfulness, and guilty rumination. The patient had no prior history or family history of depression. He also had fatigue and fears of cancer with a Hamilton Depression Rating Scale (HDRS [a quantitative measure of depression]) score of 29, indicating severe depression. Four weeks after discontinuation of vitamin A, the HDRS score dropped to 6, and the patient was completely normal 2 months after treatment. The authors concluded that this was a case of vitamin A–induced major depression. Fishbane et al[45] reported 2 cases of vitamin A toxicity in which blood levels confirmed high concentrations of vitamin A; these cases were associated with neurologic effects of drowsiness and inability to grasp objects in 1 patient, and, in the second patient, psychotic symptoms of insects crawling over the body, with the bizarre behavior of the patient trying to cut off his son's hair because he thought insects had infested his son's body. There was no prior history of psychiatric disorder and the symptoms resolved with the discontinuation of vitamin A. Haupt[46] also reported a case of psychosis with vitamin A intoxication. Frame et al[32] described a 16-year-old boy with emotional lability and loss of appetite associated with taking high doses of vitamin A. After discontinuation of the supplement, the symptoms resolved. Bifulco[42] reported a 52-year-old woman who took daily high doses of vitamin A. She developed insomnia and loss of weight and appetite. She became "completely disinterested in her surroundings and was found to brood all the time." One week after discontinuation of vitamin A, her symptoms resolved.

One of the more unusual cases of possible vitamin A overexposure is a syndrome known as *pibloktoq* suffered by people living within the Arctic Circle. This syndrome includes symptoms ranging from depression to explosive outbursts. Landy[47] proposed that this syndrome resulted from excess consumption of vitamin A due to a diet that included polar bear liver as well as various internal organs from other indigenous animals, all of which contain very high vitamin A levels. There are possible parallels with symptoms reported in Arctic explorers who, after consuming polar bear liver, exhibited symptoms including headaches nausea, drowsiness, and behavioral changes. Further, repeated ingestion resulted in a return of the symptoms, indicating a challenge/dechallenge effect.[47] Such behavioral effects of vitamin A are not surprising considering the fact that there have been multiple case reports of vitamin A intoxication associated with the neurologic disorder of benign intracranial hypertension or pseudotumor cerebri.[34,38,48–55]

Suicide and Depression in Acne Patients Treated With Isotretinoin

Individual accounts of depression following isotretinoin treatment. There are a number of cases reported in the

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literature of isotretinoin treatment being associated with depression and suicide, as well as psychosis and aggression. A list of case reports are described in Table 1. One patient[18,56] was an 18-year-old man who developed depressed mood, loss of interest, apathy, insomnia, anergia, anhedonia, and irritability, with feelings of guilt and loss of work and social function after 2 months of isotretinoin treatment. This patient attempted suicide on the fifth month of isotretinoin treatment. At the time of psychiatric evaluation, his HDRS score was 31, representing clinically significant depression. He had been receiving trazodone for the prior 6 weeks without benefit and was still on isotretinoin at the time of the suicide attempt. After discontinuation of isotretinoin and administration of fluoxetine, there was an improvement in mood over 4 weeks, with an HDRS score of 5 at follow-up. A second patient[18,56] was a 20-year-old women treated with isotretinoin who developed depression, tearfulness, suicidal ideation, feelings of worthlessness and agitation, anergia and anhedonia, irritability, and anger. Her HDRS score was 29. The patient also had symptoms of headache. Following supposed discontinuation of isotretinoin and treatment with imipramine and several other antidepressants, the patient exhibited a poor response. She later revealed that she had been surreptitiously continuing the isotretinoin, but, after she finally stopped and fluoxetine was started, she had a reduction of symptoms within 2 weeks and a follow-up HDRS score of 8. A third patient was reported to have several months of symptoms of depressed mood, irritability, aggression, agitation, decreased sleep, decreased appetite, reduced concentration, anhedonia, and early morning awakening that began during a course of isotretinoin therapy. These symptoms resulted in the breakup of her marriage. At the time of the evaluation, she continued to have depressive symptoms even though she had not been taking isotretinoin for 10 months. Her HDRS score was 26, consistent with clinically significant depression, and fell to 9 five weeks after administration of an antidepressant, indicating successful treatment of depression. The authors described 3 other cases that resolved with discontinuation of isotretinoin[18,56]

Bravard et al[57] described a 17-year-old with a prior history of depression treated with isotretinoin at 0.5 mg/kg/d. At the time of treatment initiation, he was free of signs of depression. However, following a further 4 months of treatment he tried to commit suicide by shooting himself. He reported that, before the suicide attempt, he had 2 months of fatigue, insomnia, and unhappy thoughts. In another case,[57] a 17-year-old male adolescent without prior psychiatric history who was treated with isotretinoin at 1 mg/kg/d developed growing fatigue, which forced him to stop sports, and, after 4 months, he developed unhappy thoughts and asked to stop treatment. It was later learned that he committed suicide 3 months after stopping treatment. Another young woman[57] with no psychiatric history began having crying spells after 3 months of isotretinoin treatment that lead to cessation of treatment.

Not all cases of depression concurrent with isotretinoin treatment are associated with suicidal ideation, but they can include a multiplicity of unusual, sometimes extreme, behaviors. For instance,[58] a 15-year-old girl who was previously without psychiatric history developed strange behavior 1 month after initiating treatment with 1 mg/kg/d of isotretinoin, including cutting the hair off of one side of her head, showing personality changes to her family, and leaving home. At that time she developed sleep disturbances and irritability and became sullen and withdrawn. At that point the medication was stopped because of symptoms of depression. Two days later, she threatened to cut her wrists and set fire to her clothes. After several months of being off of the medication, she was reported to be normal again. The authors reported another case of depression that alleviated with cessation of the drug. A number of other cases, most of which resolved with discontinuation of treatment (dechallenge) and some that returned with rechallenge, have been described in the literature and are not described in detail here. These reports are summarized in Table 1.[16,17,56–82]

Isotretinoin has also been associated with symptoms of mania and psychosis.[63,69,83] Two male and 3 female acne patients with no prior history of psychiatric diagnosis and with a mean age of 19 years reported "manic psychosis" with their symptoms developing after a mean of 8 months (range, 3–11) following start of treatment with isotretinoin. Four patients had an improvement in symptoms with antipsychotic treatment while 1 was treated with antipsychotics without a response. Three patients attempted suicide at some time after initiation of treatment.[79] This drug may also exacerbate preexisting psychiatric conditions[63,69,77]; for instance, Schaffer et al[82] examined the charts of 300 patients with bipolar disorder. Ten of the patients were found to have been treated with isotretinoin. Of those, 9/10 had an exacerbation of their psychiatric symptoms with treatment, and 3 developed suicidal ideation. In the 9 patients, 6 had a mixed depressive and manic response, 1 was hypomanic, and 2 were depressed. Symptoms began from 4 to 20 weeks after initiation of therapy and resolved with discontinuation in all but 1 patient.

The evidence from the literature hence shows that isotretinoin treatment affects individuals in differing ways, but, even though the diversity and severity of symptoms vary, all have adverse effects on the mental well being of these individuals. The physiologic effects of isotretinoin are presumably on pathways that are part of the pathology of these psychiatric conditions but with the most prominent effects being on those pathways that engender depression.

The evidence of an isotretinoin-depression association from group studies. In one series[71] of 121 isotretinoin-treated patients, 5 (4%) developed persistent depression; 31 (26%) developed fatigue. In another series,[60] 6 of 110 of isotretinoin-treated (1–2 mg/kg/d) patients (5.5%) developed symptoms of depressed mood, crying spells, malaise, and forgetfulness. Of these 6 patients, 4 were women and 2 were men, with a mean age of 28 years, while 1 patient had a prior history of depression. Isotretinoin was discontinued in 1 patient because of depression and forgetfulness. In another report,[59] 10 of 94 isotretinoin-treated patients (11%) developed depression. In patients treated with high doses (> .75 mg/kg/d), 7%

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Table 1. Case Reports and Case Series of Depression and Suicide Associated With Isotretinoin

Study	Subjects, N[a]	Depression, n	Suicidal, n	Psychosis, n	Violence and Aggression, n	Past Psychiatric History, n[b]	Time to Depression Onset/Suicide After Treatment Initiation	Dechallenge, n	Rechallenge, n
Hazen et al,[60] 1983	6/110	6	0	0	0	1 (5)	2 wk	6	0
Bruno et al,[59] 1984	10/94	10	0	0	0	NR	1 mo	10	0
Lindemayr,[61] 1986	1	1	1	0	0	NR	2 mo	0	0
Burket and Storrs,[62] 1987	1	1	0	0	0	NR	20 wk	1	0
Bigby and Stern,[63] 1988	3	3	1	0	0	NR	6 wk, 2 mo	1	0
Villalobos et al,[83] 1989	1	0	0	1	0	NR	2 wk	1	1
Scheinman et al,[64] 1990	7/700	7	1	0	Irritability	2 (5)	During treatment	7	1
Hepburn,[65] 1990	1	1	1	0	1	NR	2 mo	1	0
Gatti and Serri,[66] 1991	1	1	1[c]	0	0	NR	1 mo after treatment	0	0
Bravard et al,[57] 1993	3	3	2[d]	0		0 (3)	2 mo, 3 mo (n = 2)	1	0
Duke and Guenther,[58] 1993	2	2	1	1	1	0 (2)	1 mo (n = 2)	2	0
Byrne and Hnatko,[56] 1995	3	3	2	0	0	0 (3)	During treatment	3	0
Aubin et al,[67] 1995	1	0	1	0	0	NR	1 d	0	0
Cotterill and Cunliff,[68] 1997	2	0	2[c]	0	0	NR	2 mo	0	0
Byrne et al,[17] 1998	3	3	1	0	3	1 (2)	During Rx, 2 mo, 10 mo after treatment	2	0
Cott and Wisner,[69] 1999	1	1	0	1	0	1	4 wk	1	0
Middelkoop,[70] 1999	1	1	1[c]	0	0	NR	During treatment	0	0
Hull and Demkiw-Bartel,[70] 2000	5/121	5	0	0	0	1 (4)	2 wk	0	0
Pitts,[72] 2000	41	41	0	0	0	NR	During treatment	41	41
Ng et al[73] 2001	1	1	1	0	1	0 (1)	2 wk	1	1
Wysowski et al,[74] 2001	431	394	37[c]	0	0	8	During treatment	0	0
Ng et al,[75] 2002	5/174	5	0	0	0	NR	During treatment	1	0
Robusto,[76] 2002	1	1	0	0	0	NR	During treatment	0	0
Van Broekhoven et al,[77] 2003	1	1	1[c]	0	0	1	During treatment	0	0
La Placa,[78] 2005	1	1	0	0	1	NR	5 wk	0	0
Barak et al,[79] 2005	5/500	0	0	5	0	3 (2)	3–11 mo	4	0
Bachmann et al,[80] 2007	1	1	0	0	0	0 (1)	6 mo	1	1
Cohen et al,[81] 2007	2/100	2	0	0	0	NR		0	0
Schaffer et al,[82] 2010	9/10	7	3	0	0	NR	4–20 wk	8	0

[a]Values with virgule construction represent n/N.
[b]Values in parentheses indicate number of subjects who did not have a past psychiatric history.
[c]Committed suicide.
[d]One of the 2 patients committed suicide.
Abbreviation: NR = not reported.

reported insomnia; 22%, fatigue; 11%, headache; 7%, weight loss; 2%, impotence; and 9%, loss of libido, while no subjects with untreated acne reported these side effects. In a clinical trial of 700 patients treated with isotretinoin, 7 developed depression; two were male and 5 were female, and their mean age was 32 years.[64] The diagnosis of depression was made on the basis of patient self-report, with confirmation by a psychiatrist in 3 of the patients; in the other 4 patients, the symptoms resolved with discontinuation of medication before there was a chance for a psychiatric interview. In 5 of 7 patients, the symptoms of depression developed during the first course of treatment with the medication; the other patients had 1 or 2 prior courses of treatment with isotretinoin. Patients reported symptoms of depression following administration of isotretinoin, including fatigue, irritability, sadness, decreased concentration, crying spells, loss of motivation, forgetfulness, and loss of pleasure. One patient had suicidal ideation. Symptoms resolved in all cases after discontinuation of medication within 2–7 days.

In another study,[75] 5/174 isotretinoin-treated versus 0/41 antibiotic-treated patients developed depression and dropped out of the study or were withdrawn from treatment by their dermatologists. Two of the patients who developed depression with isotretinoin were evaluated by a psychiatrist and were felt to have concurrent psychosocial stressors, while 3 refused to be evaluated by a psychiatrist. Of these 3, no concurrent stressors were identified in 2, and 1 had a remission of symptoms with discontinuation of isotretinoin. A study of members of the Israeli armed services looked at 1,419 conscripts who had used isotretinoin[84] and found a statistically significant increase in suicidal thoughts and suicide attempts as well as a significant increase in mental health services utilization in those individuals compared to controls.

Not all studies, though, have shown a clear link between isotretinoin use and depression. In 132 subjects treated with isotretinoin or antibiotic, scores on the Center for Epidemiologic Studies Depression scale, a measure of depression, went from 8.1 to 6.6 in the isotretinoin group and from 9.3 to 8.4 in the antibiotic group.[85] Although no statistically significant changes with treatment were reported, the authors nevertheless stated that "treatment of acne either with conservative treatment or isotretinoin was associated with a decrease in depressive symptoms."[85(p557)] In a study[86] of 45 Turkish patients treated for acne with 0.5–1 mg/kg for 16 weeks, there was no change in depression as measured with the Montgomery-Asberg Depression Rating Scale. Only 23 patients completed treatment. Kaymak et al[87] studied 100 Turkish acne patients before and after treatment with isotretinoin at 0.75–1.0 mg/kg. Patients had an increase in depressive scores measured with a Turkish version of the HDRS after 3 months of treatment with 1 patient developing clinically significant depression. Depression ratings decreased from 3 to 6

months of treatment. The authors suggest that these changes might be part of a clinical effect of isotretinoin; however, they differ from other accounts of isotretinoin-associated depression in that depression resolves while the subject is still using isotretinoin. In a second study[88] from this group, acne patients were given either isotretinoin (N = 37) or topical treatment (N = 41). After 4 months, a quantitative measure showed better quality of life in the isotretinoin group, and, at 4 months, there were also better scores for depression as measured with the Beck Depression Inventory (BDI). Rehn et al[89] studied 126 acne patients treated with isotretinoin. There was no increase in depressive symptoms in the group as a whole as measured with the BDI. One patient attempted suicide. Kellett and Gawkrodger[90] studied 33 patients at baseline and after 8 and 16 weeks of isotretinoin treatment. There was no effect of isotretinoin on depression, either increased or decreased, as measured with the BDI.

Strauss et al[91] studied 300 acne patients given 1.0 mg/kg isotretinoin and 300 patients given 0.4 mg/kg micronized isotretinoin. Eleven patients in the micronized isotretinoin group had psychiatric side effects, and 4 had to drop out for depression and/or mood swings, with the symptoms improving with cessation of treatment. One patient in the regular isotretinoin group had depression requiring cessation of treatment, which resolved after removal of the drug. The apparently higher rate of depression in the group receiving micronized isotretinoin raises the question of whether the higher bioavailability of isotretinoin in this form is associated with an increased risk of depression.

Schulpis et al[92] studied 38 patients with cystic acne before and after 30 days of treatment with 0.5 mg/kg isotretinoin and compared them to 30 controls. Subjects were assessed with the Profile of Mood States, Hopkins Symptom Checklist, and the National Institute of Mental Health (NIMH) Mood States Questionnaire (MSQ). Although cystic acne patients had elevated levels of depression and anxiety at baseline compared to controls, isotretinoin had no effect on symptoms of depression. Only the NIMH MSQ showed significant reductions in anxiety with treatment.

Cohen et al[81] studied 100 acne patients treated with isotretinoin and 41 treated with oral antibiotics and 59 treated with topical creams. Subjects were evaluated before and after treatment with the Center for Epidemiologic Studies Depression scale and the Zung Depression Status Inventory. Zung Depression Status Inventory scores increased from 30 to 31.5 in the group as a whole, with no significant difference between groups. Two patients in the isotretinoin group became depressed with treatment as defined by a Center for Epidemiologic Studies Depression scale score higher than 15; no one in the control group became depressed. The authors failed to report Zung score before and after treatment by treatment group, although the *P* value reported of .2 suggested that, with a larger sample size, the difference could have been significant.

Thus, there is disparity between studies, most likely due to variability in techniques and limitations in sample size. Analysis of the 4 largest studies, though, showed an association between isotretinoin treatment and depression that ranged from 1%[64] to 2%[81] to 4%[71] to 6%[60] to 11% of patients.[59] Some of the studies that showed a lower frequency of association included results that relied on self-reporting, and it has been described that subjects report behavioral changes such as decreased school or work performance or impulsivity with less frequency than do family members.[93] In studies that report no difference in mean scores on measures of depression, it is possible that the fact that most people were not affected by the drug obscures the fact that the drug is affecting a select number. Overall, these studies do not have large enough sample sizes to address the question at hand, given the fact that most patients taking isotretinoin do not develop depression. Nevertheless, there is a consistent pattern of cases of depression developing in a subpopulation of patients taking isotretinoin in these studies.

The evidence of an isotretinoin/depression association from large databases studies. Studies analyzing large databases have been used to assess the relationship between isotretinoin and depression. In one study funded by the manufacturer of isotretinoin,[94] a retrospective study from a database of 2,281 patients who had used isotretinoin and/or an antidepressant, found that patients treated with isotretinoin were no more likely to receive an antidepressant than those not using isotretinoin. However, this study is limited by the possibility that dermatologists may stop isotretinoin in the setting of depression without antidepressant treatment or that patients may refuse psychiatric referral or treatment. In the study by Ng and colleagues,[75] this was in fact the case of all 5 patients who developed mood changes on isotretinoin. In another study funded by the manufacturer,[15] medical data were examined for the association between isotretinoin use and the frequency of suicide, attempted suicide, and "neurotic and psychotic disorders" in patients in the United Kingdom and Canada; no increase was found in these parameters with isotretinoin treatment. Wysowski[95] pointed out limitations of this study, including the lack of standardized diagnosis or inclusion of data on psychoactive drug treatment, lack of patient interview for depression, underascertainment of suicides (the death certificate data were not examined), lack of data on acne severity, lack of control group, absence of information about length of treatment, differences in prescribing between the United Kingdom and Canada, and the limited sample size for the UK sample. Another study[96] involved an analysis of the United Health care database. Although a published abstract from 2001 showed no increase in coding for depression in isotretinoin users,[96] if instead coding for diagnosis of depression and/or antidepressant prescription is used to compare control and isotretinoin-treated groups then a statistically significant increase in depression is evident in isotretinoin-prescribed patients.

Azoulay et al[97] studied a group of patients in Quebec who, between 1984 and 2003, had obtained an isotretinoin prescription. Cases were defined as individuals who were diagnosed or hospitalized for depression and who filled a prescription for an antidepressant within 30 days after the

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diagnosis or hospitalization. Subjects who received an antidepressant in the prior 12 months were excluded. Rates of exposure to isotretinoin in the 5 months before the event were compared to a 5-month control period. Of 30,496 subjects examined, 126 met criteria. The adjusted relative risk of depression after receiving isotretinoin was 2.68 (95% CI, 1.10–6.48), a finding that provides a strong case for the increased risk of depression with isotretinoin treatment.[97]

An analysis of reports of adverse drug reactions was performed by using data from Roche, the World Health Organization (WHO), and the United Kingdom Medicines Control Agency from 1982 to 1998.[70] This found that the association between isotretinoin and suicides or psychiatric adverse events is much greater than that of antibiotics when used for acne treatment; 60% of all adverse psychiatric events associated with acne treatment were coupled with isotretinoin use despite the fact that antibiotics are employed more frequently than isotretinoin. Detailing the numbers from the WHO, there were 47 reports of suicide, 67 attempted suicides, and 56 cases of suicidal ideation.[70] Description of the reported psychiatric symptoms included mood swings, depression, amnesia, anxiety, and insomnia as well as suicide.

The FDA reported 431 adverse drug reactions for isotretinoin between the years 1982 and 2000.[16] Of the patients with adverse drug reactions, 37 had committed suicide, 110 were hospitalized for depression, suicidal ideation, or suicide attempts, while 284 suffered depression without hospitalization. The Adverse Events Reporting System database placed isotretinoin as the fifth-ranking drug for reports of serious depression and the fourth-ranking drug for depression.[16] For attempted suicide, isotretinoin ranks number 10, and it is the only nonpsychiatric drug that ranks in this top 10 list. A study[98] of the adverse drug reactions from the FDA also suggests a challenge/dechallenge effect for isotretinoin, with remission of depression resulting between cessation and restarting the drug. When the 2002 FDA reports were examined, 3,104 cases of psychiatric adverse effects were found for isotretinoin, 173 of which were suicides.[98]

A 2004 analysis of the FDA's MedWatch database showed that, between 1989 and June 2003, there were 216 reported drug-linked suicides in children and adolescents younger than 18 years.[99] Of these, 72 suicides were linked to isotretinoin. The FDA states that MedWatch reflects as few as 1% of actual adverse drug events,[16] which means that 72 isotretinoin suicide reports could represent as many as 7,200 suicides.

A number of drug regulatory bodies from countries outside of the United States have reported psychiatric side effects of isotretinoin administration. For example, the Canadian Adverse Drug Reaction Monitoring Program reported[100] 16 psychiatric reactions with isotretinoin, including depression (5), aggressive reaction (4), emotional lability (4), irritability (3), suicidal tendency (3), amnesia (2), abnormal thinking (1), aggravated depression (1), manic reaction (1), and suicide attempt (1). In the reports that indicated an outcome, 7 patients recovered with discontinuation of isotretinoin, 3 recovered with residual effects, and 1 had not yet recovered at the time of reporting. Two hundred twenty-two adverse events were reported[101] to Health Canada between 1983 and 2002, and 56 (25%) of these were psychiatric adverse events and included depression and suicidal ideation. An analysis[102] of a subset of Canadian adverse drug reactions reported in children from 1998 to 2002 showed that isotretinoin was the medication most commonly associated with adverse drug reactions. Of 1,193 reported adverse drug reactions, 56 were for isotretinoin, including 2 deaths and 26 cases of psychiatric adverse drug reactions. The Australian Adverse Drug Reactions Committee, between 1985 and 1998, cataloged 129 reports of adverse reactions, 12 of which included depression.[103] In 4 cases, there were symptoms of psychosis. Three patients had suicidal thoughts, 2 attempted suicide, and 1 completed suicide. Three recovered with withdrawal of isotretinoin and 1 with antidepressant.[103] The Irish Medicine Boards, between 1983 to 1988, received 6 reports of depression associated with isotretinoin treatment, 1 of which was suicide.[104] As of June 2005, the Australian Adverse Drug Reaction Committee had received 21 reports of either suicide attempts or suicidal ideation with isotretinoin use, 1 of which led to a coronial investigation.[105] The Danish Medicine Agency, between 1997 and 2001, recorded 34 psychiatric adverse events with isotretinoin treatment, 23 of which included depression.[106]

Studies from databases allow trends to be observed in a large population, and a number of these analyses link the use of isotretinoin to an increased occurrence of depressive behavior and suicide. The lack of a finding of an association between isotretinoin in some of the studies may be due to the lack of standardized diagnosis, lack of patient interview for depression, underascertainment of suicides, and the absence of control groups. The relatively small increase in risk of depression, for instance from the Azoulay et al[97] study, which found a 2.68-fold rise, most likely explains why this increase was not always significant.

Positive behavioral effects of isotretinoin—improved self-image does not cure depression. The dermatology literature has frequently emphasized the potential for positive behavioral effects with isotretinoin because of the effectiveness of this drug in clearing acne.[107–110] Although acne is associated with a decrease in self-esteem, anxiety about appearance, and unhappiness about appearance,[111–113] studies have not been able to demonstrate a correlation between symptoms of clinical depression and objective severity of acne or an improvement in clinical depression with treatment. Furthermore, although studies have shown improvements in self-esteem and anxiety about appearance with acne treatment, they have not clearly shown an increase in actual cases of depression based on standardized structured clinical interviews in noncystic acne patients. For instance, studies have not shown an association between dermatologic conditions and psychiatric disorders in long-term care psychiatric patients.[114]

Some studies[115] have found higher levels of trait and state anxiety in cystic and noncystic acne compared to normal controls or higher levels of social anxiety in patients with

severe acne.[116] However, a larger number of studies have not been able to show abnormal levels of anxiety in acne patients or a correlation between acne severity and anxiety measured with the State-Trait Anxiety Inventory[117] or other measures of psychological distress or quality of life.[118–123] Studies have not shown a significant effect of isotretinoin treatment on measures of anxiety and depression[20,124,125] or have shown only a modest effect on only one of multiple measures of anxiety and depression.[123,126]

A recent study[127] looked at 244 high school students at baseline and at 6 and 12 months; there was no relationship between presence of acne or acne severity and measures of depression or anxiety. Furthermore, there was no evidence of a causal role for acne in the development of symptoms of depression or anxiety.

Some of the dermatology literature, however, has selectively cited studies to support the idea that acne causes depression and that treatment leads to an improvement in depression. For instance, one of the most cited studies[113] involved only 10 patients with acne assessed with a nonstructured psychiatric interview and measures of depression, with no control group and no statistics reported. Two patients were reported as no longer having depression after treatment, while depression persisted in one. Another report[128] from these authors involved 480 dermatologic patients, including 72 with noncystic acne. Six percent of the acne patients reported suicidal ideation, which is higher than the 3% of general medical patients reporting suicidal ideation. Patients with acne had higher Carroll Rating Scale for Depression scores than patients with other dermatologic conditions (atopic dermatitis, alopecia, outpatient psoriasis), with the exception of inpatients with psoriasis, a difference that was statistically significant. However, this study did not involve nonmedical controls.

In short, these studies provide a strong indication that there is an improvement in self-image following isotretinoin treatment for acne. However, they do not support the conclusion, often repeated in the dermatology literature, that acne results in clinical depression or that treatment of acne with isotretinoin leads to an improvement in clinical depression.

The temporal relationship between isotretinoin treatment and depression. The fact that the development of depression is temporally related to the initiation of treatment with isotretinoin supports the causal role that isotretinoin plays in the development of depression. Most cases of isotretinoin-associated depression developed after 1–2 months of treatment.* In other cases, depression or suicide occurred at later stages of treatment, around 2–4 months after drug commencement. Temporal analysis of these reports, though, can be difficult, as these details are not always provided and symptoms possibly not fully reported.[56,57,64,68,74,75,79] This may explain the case of Gatti and Serri,[66] who developed depression and social problems 1 month after discontinuation of a 4-month course of treatment and killed himself 3 weeks later. Similarly, Bravard et al[57] described a case of depression after 3 months of treatment, with completed suicide 3 months after the end of treatment. From the case reports and data of Wysowski et al,[74] it appears there is a longer lag time between initiation of isotretinoin therapy and committed suicides (3 months) than the first onset of depressive symptoms (1 month), possibly because patients suffer in silence with depression for some time before they commit suicide. One case of suicide on the first day of isotretinoin treatment does not fit the profile of other cases and was unlikely to have been related to the drug.[67]

Overall, review of these cases indicates that depression and suicide do not follow immediately after treatment but commonly 1–2 months after commencement, sometimes with a longer delay. This suggests that the biologic mechanism may not be via immediate influence of isotretinoin on a crucial neurotransmitter or other signal pathway but may be through a secondary system or possibly alteration of neuroplasticity or metabolic process known to be influenced by retinoic acid, as previously described[28] and discussed below (see Biologic Plausibility). Alternatively, changes in neurochemical systems may occur more rapidly, but it may take weeks or months before a behavioral effect is seen, as is the case with the mechanism of action of antidepressants.

There have been multiple reports in the literature of depression associated with isotretinoin use that resolved after discontinuation of the drug and, in some cases, returned with reintroduction of the drug.[56–58,62,63,75] For instance, the FDA has 41 reports of positive challenge/dechallenge/rechallenge with isotretinoin,[129] and 67% of these are not associated with a psychiatric history. In 1 series of 7 cases of depression associated with isotretinoin treatment,[64] symptoms resolved in all cases after discontinuation of medication within 2–7 days. One patient of this series returned to isotretinoin treatment and, within 3 months of this, exhibited a recurrence of depression.[79] Ng et al[73] described the example of depression in a 17-year-old male adolescent 2 weeks after he commenced isotretinoin treatment and showed improved symptoms following a reduction in isotretinoin dose as well as application of an antidepressant (sertraline). When the dose of isotretinoin was increased again, the depressive symptoms returned, in spite of a clearing of acne, with an associated suicide attempt. When the dose was stopped, the depressive symptoms rapidly resolved. Bachmann et al[80] reported a case of a 16-year-old boy who developed symptoms of depression that resolved after discontinuation of isotretinoin. Review of his history showed that he had an episode of isotretinoin-associated depression that resolved 3 years earlier after discontinuation of the drug.

In another series, several cases were described,[16] including a 19-year-old man with no psychiatric history who, during a 3- to 4-month course of isotretinoin therapy, developed personality changes, mood swings, and depression. After completion of treatment, he returned to normal. The patient started a second course of isotretinoin treatment at a later date. Again he experienced the same symptoms but returned

*References 13, 14, 17, 56–66, 69–71, 73, 74, 76, 78, 83, 93.

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to normal at the end of 4 months of treatment. Sometime later, he started a third course of treatment. This time his symptoms recurred and persisted after the end of isotretinoin treatment. A year later, he was referred for counseling. In a second case, an 18-year-old man with no history of mental disorder received 1.1 mg/kg/d of isotretinoin. After 29 days, he experienced depression, loss of interest in daily activities, and decreased school performance. Isotretinoin was stopped and symptoms cleared in 8 days. The drug was started at 0.5 mg/kg/d, and the symptoms returned after 5 days. Isotretinoin was stopped, and the symptoms cleared in 7 days. He later was treated at the lower dose without recurrence of symptoms. The report concluded that multiple lines of evidence pointed to an association between isotretinoin treatment and depression.

These examples of depression resulting from isotretinoin use, remission on discontinuation of the drug, and, in some cases, the return of depression on reintroduction of isotretinoin make a very strong case for their link in some individuals. It also implies that, although the promotion of depression by isotretinoin is relatively slow, the biologic change can, in some cases, be restored to normal when the drug is removed.

Dose-response relationship between isotretinoin treatment and depression. The fact that higher doses of isotretinoin are associated with a greater risk of depression is further indication that isotretinoin is responsible for the development of depression. For example, when doses were as high as 3 mg/kg/d, which is 3–6 times higher than the standard dose, then 25% of patients[93] exhibited depression, a result that contrasts with the 3%–4% that is described in several other reports. One case[93] involved a lawyer who was no longer able to argue cases in court, and a man who precipitously divorced his wife. The author concluded that the "psychological changes may be dose related." The presence of a dose-response relationship would also predict that a decrease in isotretinoin dose would reduce symptoms of depression, and a "possible dose response" was evident in 6 cases in which isotretinoin dose was reduced and depression symptoms declined.[129] In another case,[73] symptoms of depression with isotretinoin improved with reduction of isotretinoin dose combined with sertraline treatment. When the dose of isotretinoin was increased again, the depressive symptoms returned, in spite of a clearing of acne, with an associated suicide attempt. When the dose was stopped, the depressive symptoms rapidly resolved. In another study,[59] higher doses of isotretinoin were associated with symptoms of depression, including depressed libido (9% of high dose versus 2% of low dose), impotence (2% versus 0%), and weight loss (7% versus 0%). These symptoms were higher than a group of acne patients not on isotretinoin, who reported none of these symptoms.[59]

These studies provide some evidence for a dose-response effect for isotretinoin and psychiatric side effects in which higher doses are associated with more side effects. A dose response has been established related to isotretinoin for other nonpsychiatric side effects, like mucocutaneous side effects,[130] using dosages of 1.0–3.3 mg/kg/d. However, these early studies of different dosing levels did not use specific measures of behavior, and current practice employs lower doses in a more restricted range (0.5–1 mg/kg/d). This lack of specific measures combined with the fact that cases of depression are not common makes it difficult to measure a dose-response relationship for psychiatric side effects related to isotretinoin.

Biologic Plausibility

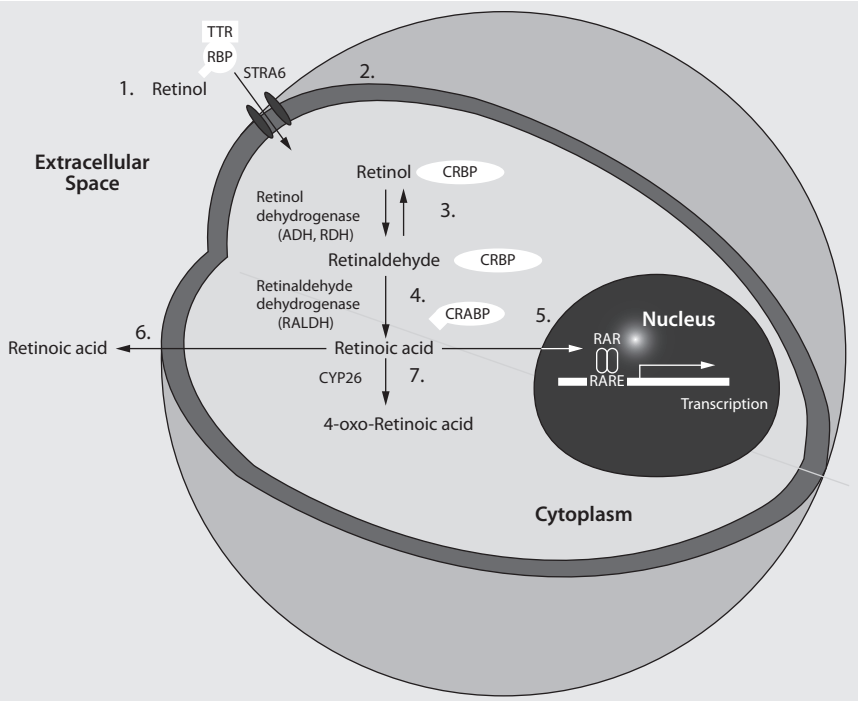
In order for a drug to cause a particular adverse event, there needs to be a plausible mechanism of action. Since depression is a disorder that is based in the brain, isotretinoin must have an effect on brain function.[28]

We will first briefly describe how retinoic acid influences gene expression in cells of the nervous system, then describe new results on retinoic acid signaling in the hypothalamus, a brain region linked with depression. Finally, two potential metabolic pathways associated with depression, and which are disrupted by isotretinoin, are discussed.

Retinoic acid signaling. As previously described, all-*trans* retinoic acid is an endogenous regulator of gene expression acting via specific receptors that function as ligand-activated (in this case retinoic acid) transcription factors. The dietary substrate of retinoic acid is vitamin A, stored as a reservoir of retinyl esters in the liver. These retinyl esters can be hydrolyzed and the resulting retinol released, and, in circulation, the retinol is bound to retinol-binding protein and transthyretin. The events that lead to activation of gene expression in a cell are shown in Figure 1. Uptake of retinol by target cells is facilitated by the retinol-binding protein receptor STRA6.[131,132] Intracellular retinol is bound to cellular retinol-binding protein before being oxidized to retinal by the ubiquitous enzymes alcohol dehydrogenase or retinol dehydrogenase. Retinal is further oxidized to retinoic acid by retinaldehyde dehydrogenase, an enzyme that is expressed only in regions where retinoic acid is required. Retinoic acid is bound to cellular retinoic acid–binding protein and translocates to the nucleus where it binds to retinoic acid receptors that form heterodimers with retinoid X receptor. These ligand-receptor complexes are bound to the retinoic acid response elements located in the promoter regions of certain genes and promote transcription. This signaling system can be inactivated by the cytochrome P450 enzyme CYP26, which generates further oxidized derivatives, including 4-oxo-retinoic acid. A balance of retinoic acid synthesis and catabolism in the cell maintains the correct levels of retinoic acid-regulated transcription. Exposure of the cells to isotretinoin, which is isomerized in tissue to the active all-*trans* retinoic acid,[10,11] will destabilize this balance and result in inappropriate gene transcription.

Retinoic acid function in the hypothalamus. Brain regions that are endogenously regulated by retinoic acid and which may be disrupted by isotretinoin to potentially promote depression have been described in our previous review and include the striatum, hippocampus, and frontal cortex.[28] An area of the brain, however, that has been little considered

Figure 1. Cellular Retinoic Acid Signaling[a]



[a](1) Retinol in the circulation is bound to retinol-binding protein (RBP), which itself is bound to transthyretin (TTR). (2) Retinol enters the cells, which may be assisted by the membrane protein STRA6. (3) Retinol in the cell is bound by cellular retinol-binding protein (CRBP) and can then be oxidized to retinaldehyde by an alcohol dehydrogenase or retinol dehydrogenase in a reversible reaction. (4) Retinaldehyde is oxidized irreversibly to retinoic acid by a retinaldehyde dehydrogenase. (5) Retinoic acid may then enter the nucleus to bind to retinoic acid receptors (RAR) to activate transcription or (6) leave the cell to act on adjacent tissue. (7) Alternatively, the system may be turned off by further oxidation of retinoic acid to oxidative metabolites, including 4-oxo-retinoic acid.

Abbreviations: ADH = alcohol dehydrogenase, CRABP = cellular retinoic acid–binding protein, RARE = retinoic acid response elements, RDH = retinol dehydrogenase.

for retinoid action is the hypothalamus. The hypothalamus is the hormone regulatory center of the brain and, as part of the hypothalamus-pituitary-adrenal axis, is a central component in the response to stress. Hyperactivity of this system is a reproducible finding in depression. Although several elements of the retinoic acid synthetic pathway had been previously identified in the hypothalamic regions of Siberian hamsters as a measure of photoperiodic change,[133] it was not recognized that endogenous retinoic acid could be synthesized and function in this region. Shearer et al[134] identified the crucial retinoic acid synthetic retinaldehyde dehydrogenase enzymes in the processes of tanycytes, the specialized ependymal cells that provide a boundary between the cerebrospinal fluid in the third ventricle and neural cells of the hypothalamus, where retinoic acid receptors and retinoid X receptor γ are found to reside. As illustrated in Figure 2, retinol present in the cerebrospinal fluid can be taken up by the tanycytes, with cellular retinol-binding protein carrying this substrate within the cell to the retinoic acid synthetic enzymes. Retinoic acid can be released into the hypothalamus via the long processes of the tanycytes that reach into the hypothalamus and regulate a number of genes including the retinoic acid receptor β as well as adrenocorticotropin-releasing hormone.[134] It was found in this same study that photoperiod regulates retinaldehyde dehydrogenase in tanycytes as well as retinoic acid receptors/retinoid X receptors in the hypothalamus, therefore showing changes in retinoic acid signaling driven by seasonal changes. Given that seasonal affective disorder is a form of depression driven by seasonality, there is the potential for retinoic acid to influence this disorder.

One particular retinoic acid–regulated gene in the hypothalamus that may provide a link between retinoic acid and depression is corticotrophin-releasing hormone,[135] a key regulatory factor in the hypothalamus-pituitary-adrenal axis[136] that may contribute to hypothalamus-pituitary-adrenal axis hyperactivity in depression.[137,138] Chen et al[139] have described increased density of retinoic acid receptor α–expressing cells in the paraventricular nucleus of patients with affective disorder, and this receptor colocalized with those neurons expressing corticotrophin-releasing hormone. Similarly, in a rat model of depression, retinoic acid receptor α levels were raised in the paraventricular nucleus.[139] These results further emphasize the importance of retinoic acid in the hypothalamus and the potential for overlap between retinoic acid regulated–hypothalamic pathways and those that underlie depression. In particular, increased retinoic acid signaling promoted by isotretinoin in the human may mimic the augmentation of this pathway resulting from the elevation in retinoic acid receptor α seen by Chen et al[139] in the paraventricular nucleus of depressed patients. This signaling provides a new mechanism by which isotretinoin may promote depression.

Metabolic effects of isotretinoin and depression. Isotretinoin administration has also been shown to affect metabolic pathways, alterations of which have been linked to depression; two examples are given below involving biotin and homocysteine. Biotin, a member of the B vitamin family (vitamin B_7) is a required nutrient that is involved in the biosynthesis of fatty acids, gluconeogenesis, and metabolism of amino acids. Side effects of biotin deficiency include hair loss, conjunctivitis, neuromuscular dysfunction, skin changes, neurologic dysfunction, and, of note for this review, depression.[140–144] For instance, Baugh[145] described a dietary-induced case of biotin deficiency resulting in anorexia, nausea, vomiting, glossitis, skin changes, and depression, while Levenson[140] described a biotin deficiency case that was associated with depression and thoughts of suicide. These symptoms went

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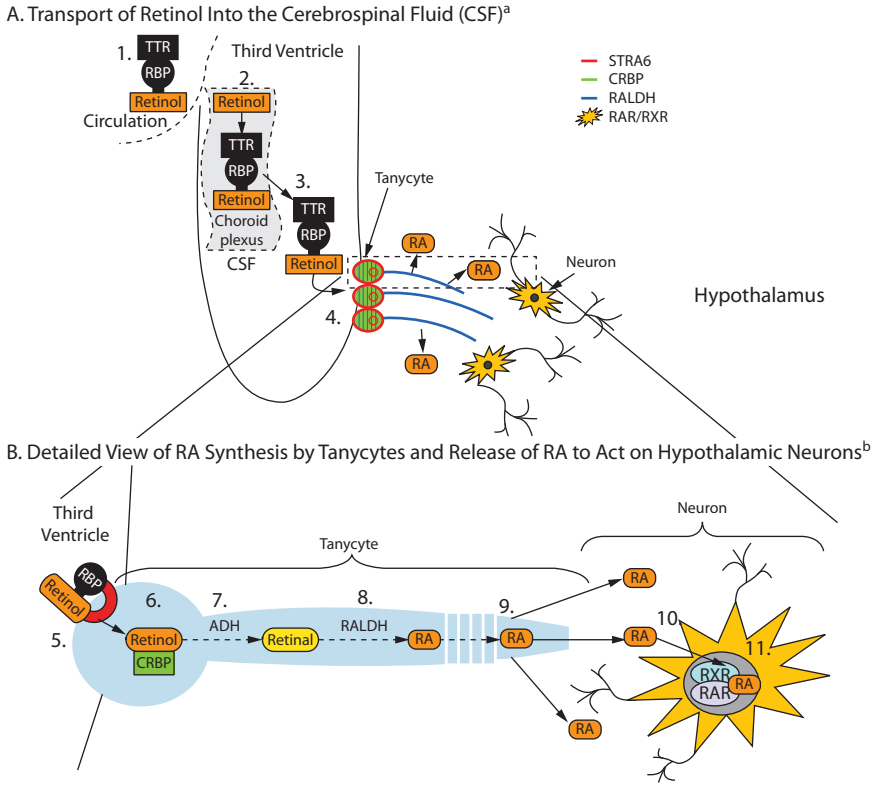
Figure 2. Retinoic Acid (RA) Synthesis and Action in the Hypothalamus



[a](1) Retinol circulates in the blood in a bound complex with retinol-binding protein (RBP) and transthyretin (TTR). (2) Retinol is taken up by the choroid plexus. (3) The choroid plexus synthesizes RBP and TTR, and these are exported into the CSF with retinol. (4) Retinol in the CSF carried by RBP and TTR is taken up by tanycytes.

[b](5) STRA6 receptors present in the membrane of the tanycyte cell bodies lining the third ventricle facilitate the uptake of retinol into these cells. (6) Intracellular retinol is bound to cellular retinol-binding protein (CRBP), and (7) retinol is converted to retinaldehyde by an alcohol dehydrogenase (ADH). (8) A retinaldehyde dehydrogenase (RALDH) oxidizes retinaldehyde to RA, and (9) RA is released by the long tanycyte processes into proximal areas of the hypothalamus. (10) Retinoic acid enters hypothalamic neurons, and (11) RA receptors in these neurons convey the RA signal to regulate gene transcription.

Abbreviations: RAR = retinoic acid receptors, RXR = retinoid X receptors.

Part A adapted with permission from Shearer et al.[134]

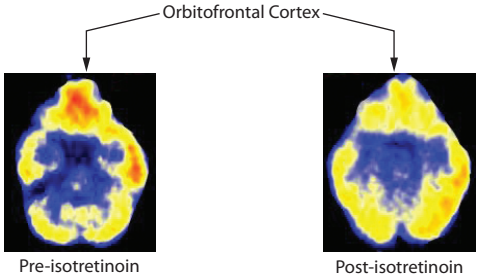
away after biotin supplementation. One mechanism by which biotin is recycled in the body, maintaining its availability, is supported by the enzyme biotinidase.[146] Mutations in this enzyme result in biotin deficiency.[141,146–152] Isotretinoin administration to human subjects is associated with a decrease of biotinidase,[153] and the presumed decrease in biotin that would result from this may contribute to depression.

Homocysteine is a sulfur-containing amino acid that is involved in carbon transfer reactions.[154] Homocysteine can receive a methyl group from 5′-methyltetrahydrofolate and become remethylated to methionine, the immediate precursor of S-adenosylmethionine, a donor of methylation reactions involved in the synthesis of DNA, proteins, phospholipids, neurotransmitters and polyamines. S-adenosylmethionine is involved in the synthesis in the brain of dopamine, norepinephrine, and serotonin, neurotransmitters that have been linked to depression,[155,156] and many studies have found a relationship between elevated homocysteine levels, lower folate concentrations, and depression.[154,157–165] Increased concentrations of homocysteine have also been associated with attacks of violent anger.[166] Isotretinoin administration to human subjects was shown to be associated with increased concentrations of homocysteine,[167] as well as decreases in 5-methyl-tetrahydrofolate,[168] providing a potential metabolic mechanism by which isotretinoin may promote depression.

Evidence of effects of isotretinoin on human brain function. The fact that isotretinoin is associated with neurologic side effects demonstrates that it has an effect on brain function. Adverse reactions are common with isotretinoin, with at least 90% of patients treated reporting at least 1 side effect.[169] Bigby and Stern[63] reviewed adverse reactions to isotretinoin reported to the Adverse Drug Reaction Reporting System between 1982 and 1985. They reported 104 side effects, which included (in decreasing frequency) skin reactions (dryness), central nervous system complaints, musculoskeletal system and pregnancy difficulties, and eye, hematopoietic, gastrointestinal, cardiorespiratory, and genitourinary disorders. Other less common side effects in this study were liver and bone abnormalities. The most common neurologic adverse reaction was headache in 11 patients. In 4 of the subjects, this was associated with pseudotumor cerebri, an idiopathic increase in intracranial pressure with papilledema and headache, and normal computerized tomography/magnetic resonance imaging and cerebrospinal fluid; a swelling of the brain that can be fatal. Headache was the most common side effect of isotretinoin after dry skin,[63] while a number of other reports have associated isotretinoin with pseudotumor cerebri.[55,170–172] The occurrence of headache with isotretinoin usage has been linked to depression,[173] suggesting that patients who show a central nervous system side effect such as headache may also be more susceptible to isotretinoin-induced depression. Certainly, these neurologic side effects are further evidence that isotretinoin can influence the brain.

There is evidence that some of the neurologic side effects are not immediately reversible. Neurologic events reported to the Norwegian Medicines Agency were assessed in patients treated with isotretinoin. There were 91 total adverse events reported from 1985 to 2005. Thirty-nine included long lasting neurologic or muscular symptoms. Long-lasting neurologic

Figure 3. The Influence of Isotretinoin on Brain Glucose Metabolism Measured by Positron Emission Tomography Fluorodeoxyglucose[a]



[a]Four months of isotretinoin treatment results in a clear decrease in orbitofrontal cortical function in this representative subject. The same subject had symptoms of headache and slight behavioral change, although not clinical depression.
Reprinted with permission from Bremner et al.[175]

symptoms, including memory loss, dizziness, headache, loss of concentration, and ataxia, were present in 17 cases. Symptoms persisted 2–18 months after stopping treatment.[174]

The influence of isotretinoin on brain metabolism has been directly investigated using positron emission tomography fluorodeoxyglucose, a technique that maps regional differences in glucose uptake in the brain. Twenty-eight subjects with acne were imaged before and after 4 months' treatment with isotretinoin or antibiotics (13 with isotretinoin, 15 with antibiotics).[175] Patients were also assessed for depression using the HDRS. This study revealed that 4 months of isotretinoin treatment led to a significant reduction in brain metabolism in the orbitofrontal cortex (Figure 3), a region that has been associated with depression.

In the case of patients reported to the Norwegian Medicines Agency, single photon emission computed tomography of the brain was performed in 15 cases who reported lasting neurologic symptoms.[174] Altered brain function was seen in all cases involving altered or reduced frontal lobe blood flow. The researchers determined that 10 of these patients had organic brain damage.

DISCUSSION

This article has outlined the evidence for a relationship between isotretinoin and depression, which includes evidence from case reports in the literature, temporal association, challenge-rechallenge studies, dose response, biologic plausibility, and class effect. According to Strom,[176] the existence of challenge-rechallenge cases alone are adequate to establish a causal link between a side effect and a drug. However, as reviewed in this article, there are a number of lines of evidence showing that isotretinoin can cause depression and suicide in some susceptible individuals.

Drug regulatory agencies worldwide are now warning patients about the risk of depression and suicide with isotretinoin, which has had an impact on prescribing behavior. Additionally, there is a growing consensus in the medical and mental health community that this is a real problem that can affect a minority of treated individuals and that patients treated with isotretinoin need to be monitored closely for psychiatric side effects and that patients and families should be fully informed of the risks and benefits of this medication.[19,177–180] Nonetheless, the dermatology community continues to incorrectly state that acne causes depression and that treating acne with isotretinoin is a treatment for depression rather than a cause of depression in some individuals. However, the evidence for an association is comparable to other drugs, such as steroids, which are accepted as being associated with psychiatric side effects.

An interesting finding from the brain imaging studies in isotretinoin-treated subjects was that the patients with headache were more likely to have decreased orbitofrontal function with isotretinoin. This finding parallels the findings of Wysowski and Swartz[173] that headache is associated with depression in isotretinoin-treated patients. It raises the possibility that subjects who are sensitive to isotretinoin-induced effects on the central nervous system, such as headache, may also be susceptible to other neural side effects of this drug, such as depression.

Studies that make use of double-blind placebo-controlled randomizations to assess the effects of isotretinoin on symptoms of depression and mood lability will be useful in the identification of factors that put individual patients at risk. The FDA recommended such studies after a 2-day meeting on the topic in 2000; however, in 2002, the FDA then advised against such a study as it would be too difficult to adequately blind because of the dry skin side effects of isotretinoin.[181] However, topical retinol can be given as a control treatment, which dries the skin, and results in minimal absorption into the bloodstream. On the basis of the literature to date, clinicians should carefully consider whether or not to rechallenge patients who have previously experienced depression while taking isotretinoin. Similarly, the treatment of patients with a psychiatric disorder, especially bipolar disorder, appears to pose a high risk for exacerbation of symptoms.

Studies performed to date have had limitations, including the use of retrospective databases with insufficient information, the lack of sufficient sample size to determine whether an effect on depression exists, lack of placebo controls and randomization, and the lack of specific standardized assessments of depression and other behaviors. Large placebo-controlled trials assessing the effects of isotretinoin on depression would be a scientific advance; however, the ethics of conducting such a trial when there is adequate aggregate information supporting a causal role of isotretinoin in the development of depression in some individuals, given the risks of the drug, is questionable.

Drug names: fluoxetine (Prozac and others), imipramine (Tofranil and others), isotretinoin (Claravis, Amnesteem), trazodone (Oleptro and others).

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